# Use of PBPK/PD Models and Foliar Transfer Coefficients in Assessing Reentry into Pesticide Treated Citrus and Turf


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## Introduction

The establishment of reentry intervals in California provided a mechanism for reducing the hazards involved in reentering pesticide treated orchards, vineyards and turf. However, current methodology for setting reentry intervals does not satisfactorily relate foliar OP residues, foliar residue transfer coefficients, percutaneous absorption and the absorbed dose to blood acetylcholinesterase (AChE) inhibition. We believe some of these issues may be resolved by the use of foliar residue transport coefficients (1, 2) in conjunction with dermal physiological pharmacokinetic/pharmacodynamic models (3, 4). This approach may also be useful for assessing the risks involved in non-worker exposures (i.e., sensitive individuals such as children) to toxic environmental residues. We present the following results obtained using foliar transfer coefficients and PBPK/PD models for parathion on citrus and isofenphos on turf.

## Methods

### *PBPK/PD Models, Isofenphos and Parathion*

A rat parathion percutaneous absorption PBPK/PD model (Fig 1) was developed using the metabolic pathway for parathion in Fig 2. P-450 $V_{max}$ and $K_m$ values were obtained from the work of Wallace and Dargan (5), tissue partition coefficients from Jepson et al. (6) for parathion and paraoxon, and in vivo [$^{14}$C-ring] parathion rat tissue data from Knaak et al. (7) for model validation. Table 1 gives the $V_{max}$ and $K_m$ values used in the model.

A rat isofenphos percutaneous absorption PBPK/PD model (Fig 3) was modified to include passes through the liver for IPS (isopropyl salicylate to salicylic acid) and SA (salicylic acid to 2-hydroxy hippuric acid) (3). The metabolic pathway for isofenphos is given in Fig 4. In vitro rat P-450 $V_{max}$, $K_m$ values (8) were used in the model and in vivo [$^{14}$C-ring] isofenphos rat tissue data (3) for model validation. Table 2 gives the $V_{max}$ and $K_m$ values used in the model.

Human liver P-450 $V_{max}$, $K_m$ values (8) for the metabolism of isofenphos were used in the human isofenphos and parathion models (Tables 1 and 2). The physiological parameters were taken from ILSI-RSI (9) for the rat and human. $V_{max}$ values were scaled to body weight ($BW^{0.7}$) in both models.

### *Transport of Foliar Residues of Parathion (Citrus) and Isofenphos (Turf) to Skin*

The dislodgeable residue transfer studies of Popendorf and Leffingwell (1) and Nigg et al. (2) in citrus were used for estimating exposure by dermal contact. A transfer coefficient ($k_d$) of 10,000 for a two-sided citrus leaf parathion residue was used (2). A transfer coefficient ($k_d$) of 10,000 was estimated for isofenphos on turf for a two-sided leaf residue (i.e., 480 Fg/h per 0.10 Fg/cm$^2$ gives a $k_d$ value of 4800 for a one-sided residue and 9800 for a two-sided residue) based on the work of Harris and Solomon (11).

### *Mass Balance for Percutaneous Absorption*

Transfer rates to skin (Fg/h) were obtained by multiplying foliar transfer coefficients ($k_d$, cm$^2$/h) by leaf surfaces residues (R = Fg/cm$^2$). The percutaneous absorption mass balance equation for simulating worker exposure to pesticide foliar residues is given below:

$dA_{surf}/dt = K_p*A*(C_{dk}/P_{sk}-C_{surf}) - K_eA_{surf} + k_dR$, pmol h$^{-1}$
$A_{surf}$ = Integ ($dA_{surf}$/dt, 0,0)
$C_{surf} = A_{surf}/V_{sk}$, pmol cm$^{-3}$
$C_{dk} = A_{dk}/V_{sk}$, pmol cm$^{-3}$
$dA_{air}/dt = K_a*A_{surf}$, pmol h$^{-1}$

where:

$K_p$ = skin permeability constant, cm h$^{-1}$
$k_dR$ = foliar dose rate to skin, pmol h$^{-1}$
A = Area of treated or exposed skin, cm$^2$

### *Inhibition of Tissue AChE, ChE, and CaE by Toxic Oxons*

In the isofenphos and parathion PBPK/PD models, 'B'-esterases [blood AChE and BChE, brain AChE, BChE and CaE, and liver CaE and BChE] are inhibited by des N-isopropyl isofenphos oxon (DNIO) and paraoxon, respectively (Figs 1 and 3). The bimolecular reaction constants ($k_i$) were calculated in the two models using literature values for $K_a$ and $k_p$ (or $k_{+2}$). Values are given in Tables 3 and 4, where $k_i = K_a/k_p$ ($k_{+2}$). The mass balance equation for the inhibition of blood AChE by DNIO and paraoxon and recovery of AChE activity is given below:

$VB * dA_{AChEB}/dt = (K_{iAChEB} * C_{AChEB} * C_{DNIOB}) - (K_{RAChEB} * A_{iAChEB})$, pmol h$^{-1}$

where:

$V_B$ = Volume of blood, L
$A_{iAChEB}$ = Inhibited AChE, pmol
$K_{iAChEB}$ = AChE bimolecular inhibition rate constant, (pmol L$^{-1}$)$^{-1}$ h$^{-1}$
$C_{AChEB}$ = Concentration of Free AChE in blood, pmol L$^{-1}$
$C_{DNIOB}$ = Concentration of DNIO/or paraoxon in the blood, pmol L$^{-1}$
$K_{RAChEB}$ = Rate of reactivation of inhibited AChE (h$^{-1}$)

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**Table 1.**

$V_{max}$, $K_m$ Values used in Percutaneous Absorption Route, Parathion

| Enzymes | Metabolism | Rat Vmax[a] | Rat Km[a] | Human Vmax[a] | Human Km[a] |
|---|---|---|---|---|---|
| **P-450** [b] | | (x10$^6$) | (x10$^6$) | (x10$^6$) | (x10$^6$) |
| Vmax1C | P to PO | 135.9 | 10.2 | 1.802 | 10.2 |
| Vmax2C | P to Ring/AP1 | 231.8 | 14.9 | 2.31 | 14.9 |
| **OP Hydrolases** [b] | | | | | |
| Vmax3C (L) | PO to Ring/AP2 | 799 | 182 | 799 | 182 |
| Vmax4C (B) | PO to Ring/AP2 | 79.9 | 182 | 79.9 | 182 |
| **Sulfate conjugation** [c] | | | | | |
| Vmax5C | NP to Sulfate | 20.0 | 50.0 | 200 | 500 |
| **Glucuronide conjugation** [c] | | | | | |
| Vmax6C | NP to Glucuronide | 5.0 | 50.0 | 50 | 500 |

[a] $V_{max}$, pmoles hr$^{-1}$ kg$^{-1}$ of BW; $K_m$, pmoles L$^{-1}$
[b] Wallace and Dargan (5)
[c] Pacifici et al., *Xenobiotica* 18, 849-856 (1988) (L) liver; (B) blood

**Table 2.**

$V_{max}$, $K_m$ Values used in Percutaneous Absorption Route, Isofenphos

| Enzymes | Metabolism | Rat Vmax[a] | Rat Km[a] | Human Vmax[a] | Human Km[a] |
|---|---|---|---|---|---|
| **P-450** [b] | | (x10$^6$) | (x10$^6$) | (x10$^6$) | (x10$^6$) |
| Vmax1C | IF to IO | 137.2 | 14.1 | 1.802 | 18.4 |
| Vmax2C | IF to DNI | 35.8 | 9.9 | 0.901 | 11.2 |
| Vmax3C | IO to DNIO | 72.6 | 9.5 | 5.457 | 11.6 |
| Vmax4C | DNI to DNIO | 25.1 | 7.9 | 0.826 | 5.8 |
| **Deaminases** [b] | | | | | |
| Vmax5C | DNI to DAI | 0.0 | 1.0 | 0.0 | 1.0 |
| Vmax6C | DNIO to DAIO | 0.0 | 1.0 | 0.0 | 1.0 |
| **OP Hydrolases** [c] | | (x 10$^6$) | (x 10$^6$) | (x 10$^6$) | (x 10$^6$) |
| Vmax7C | IO to Ring/AP1 | 3.9 | 182 | 3.9 | 182 |
| Vmax8C | DNIO to Ring/AP2 | 5.2 | 182 | 5.2 | 182 |
| Vmax9C | DAIO to Ring/AP3 | 0.0 | 182 | 0.0 | 182 |
| Vmax10C | DNI to Ring/AP4 | 0.20 | 15.0 | 0.2 | 15 |
| Vmax11C | DAI to Ring/AP5 | 0.0 | 182 | 0.0 | 182 |
| **CaE** [d] | | (x 10$^6$) | (x 10$^6$) | (x 10$^6$) | (x 10$^6$) |
| Vmax12C | IF to IFA | 0.176 | 62 | 0.176 | 62 |
| Vmax13C | DNI to DNIA | 2.7 | 62 | 2.7 | 62 |
| Vmax14C | DAI to DAIA | 0.0 | 62 | 0.0 | 62 |
| Vmax15C | IO to IOA | 0.0 | 62 | 0.0 | 62 |
| Vmax16C | DNIO to DNIOA | 0.0 | 62 | 0.0 | 62 |
| Vmax17C | DAIO to DAIOA | 0.0 | 62 | 0.0 | 62 |
| Vmax18C | IPS to SA | 0.25 | 50 | 0.25 | 50 |
| **Glycine Conjugation** | | | | | |
| Vmax19C | SA to Hippurate | 0.25 | 50 | 0.25 | 50 |

[a] $V_{max}$, pmoles hr$^{-1}$ kg$^{-1}$ of BW; $K_m$, pmoles L$^{-1}$
[b] Knaak et al. (3, 8)
[c] Wallace and Dargan (5)
[d] Talcott, *Toxicol. Appl. Pharmacol.*, 47, 145-150 (1979)

**Table 3.**

Affinity constants ($K_a$) and phosphorylation constants ($k_p$) used to describe the inhibition of tissue AChE, BChE and CaE by Paraoxon in the rat and human.

| Tissues/Enzymes [a, b] | $K_a$ (pmol L$^{-1}$) | $k_p$ (hr$^{-1}$) | $k_i$ ($k_p/K_a$) pM$^{-1}$·hr$^{-1}$ |
|---|---|---|---|
| **Blood** | (10$^6$) | | (10$^{-6}$) |
| AChE | 21.69 | 38.17 | 1.76 |
| BChE | 9.1 | 21.3 | 2.34 |
| **Brain** | | | |
| AChE | 21.69 | 38.17 | 1.76 |
| BChE | 9.1 | 21.3 | 2.34 |
| CaE | 35.0 | 20.0 | 0.57 |
| **Liver** | | | |
| BChE | 91 | 21.3 | 0.234 |
| CaE | 35.0 | 21.0 | 0.60 |

[a] Values from Wang and Murphy, *Toxicol. Appl. Pharmacol.*, 66, 409-419 (l982) used for AChE.
[b] Values from Cohen et al., *Toxicol. Appl. Pharmacol.*, 81, 452-459 (l985).
Aldridge and Reiner (1972) Enzyme inhibitors as substrates, In North-Holland Research Monographs, Frontiers of Biology, Vol. 26, p 236, Neuberger A and Tatum E: (Ed) North-Hollands Publishing Company, London.
Chiu, Main and Dauterman, *Biochem. Pharmacol.*, 18, 2171-2177 (l969) evaluated.

**Table 4.**

Affinity constants ($K_a$) and phosphorylation constants ($k_p$) used to describe the inhibition of tissue AChE, BChE and CaE by des N-isopropyl Isofenphos oxon in the rat and human.

| Tissues/Enzymes [a, b] | $K_a$ (pmol L$^{-1}$) | $k_p$ (hr$^{-1}$) | $k_i$ ($k_p/K_a$) pM$^{-1}$·hr$^{-1}$ |
|---|---|---|---|
| **Blood** | (10$^6$) | | (10$^{-6}$) |
| AChE | 102.0 | 38.17 | 0.36 |
| BChE | 43.2 | 21.3 | 0.49 |
| **Brain** | | | |
| AChE | 102.0 | 38.17 | 0.36 |
| BChE | 43.2 | 21.3 | 0.49 |
| CaE | 35.0 | 20.0 | 0.57 |
| **Liver** | | | |
| BChE | 91.0 | 21.3 | 0.234 |
| CaE | 35.0 | 20.0 | 0.60 |

[a] Values from Wang and Murphy, *Toxicol. Appl. Pharmacol.*, 66, 409-419 (1982) used for AChE.
[b] Values from Cohen et al., *Toxicol. Appl. Pharmacol.*, 81, 452-459 (1985).
Aldridge and Reiner (1972) Enzyme inhibitors as substrates, In North-Holland Research Monographs, Frontiers of Biology, Vol. 26, p 236, Neuberger A and Tatum E: (Ed) North-Hollands Publishing Company, London.
Chiu, Main and Dauterman, *Biochem. Pharmacol.*, 18, 2171-2177 (1969) evaluated.

**Figure 1.**

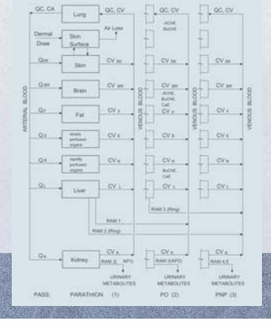
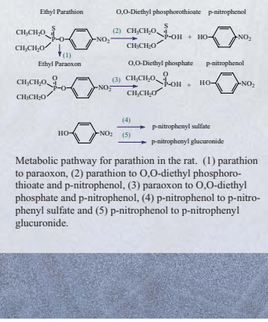



**Figure 2.**




Metabolic pathway for parathion in the rat. (1) parathion to paraoxon, (2) parathion to O,O-diethyl phosphorothioate and p-nitrophenol, (3) paraoxon to O,O-diethyl phosphate and p-nitrophenol, (4) p-nitrophenol to p-nitrophenyl sulfate and (5) p-nitrophenol to p-nitrophenyl glucuronide.

**Figure 3.**

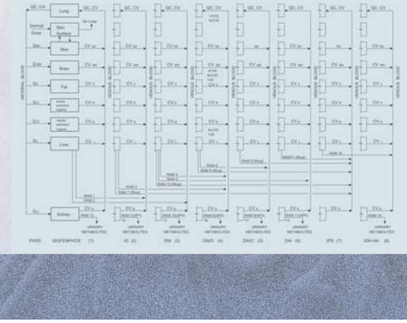
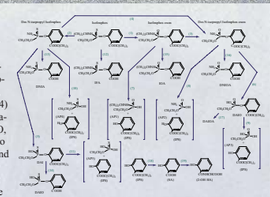



**Figure 4.**

Combined metabolic pathway for Isofenphos in the Rat, Guinea Pig and Dog (3). (RAM1) IF, isofenphos to IO, isofenphos oxon; (RAM2) IF to DNI, des N-isopropyl isofenphos; (RAM3) IO to DNIO, des N-isopropyl isofenphos oxon; (RAM4) DNI to DNIO, (RAM5) DNI to DAI, desaminoisofenphos; (RAM6) DNIO to DAIO, des aminoisofenphos oxon; (RAM7) IO to AP1, O-ethylisopropylaminophosphate and IPS, isopropyl salicylate; (RAM8) DNIO to AP2, O-ethylaminophosphate and IPS; (RAM9) DAIO to AP3, O-ethylphosphate and IPS; (RAM10) DNI to AP4, O-ethylamino-thiophosphate and IPS; (RAM11) DAI to AP5, O-ethylthiophosphate and IPS; (RAM12) IF to IFA, carboxylic acid of isofenphos; (RAM13) DNI to DNIA, carboxylic acid of DNI; (RAM14) DAI to DAIA, carboxylic acid of DAI; (RAM15) IO to IOA, carboxylic acid of IO; (RAM16) DNIO to DNIOA, carboxylic acid of DNIO; (RAM17) DAIO to DAIOA, carboxylic acid of DAIO; (RAM18) IPS to SA, salicylic acid; (RAM19) SA to 2-OH-HA, 2-hydroxy hippuric acid.



## Results

### *Parathion, material balance*

Table 5 gives the results of simulated 8 h worker exposures to foliar residues of parathion on citrus (0.1, 1.0. 5.0 and 10.0 Fg/cm$^2$, two sided leaf residue). According to the model, foliar residues of 10 Fg/cm$^2$ result in the transfer of 11.42 mg of parathion (800 mg/70 kg of BW) to the skin of workers over the course of an 8 h work day. Of the 11.42 mg deposited on skin, ~3.0% was absorbed (~50% metabolized and ~50% retained in body fat as parathion), 2% was lost to air and 95% remained as a dermal residue at the end of the work day. The parathion present in body fat was small (1.3%) at the end of the first day (i.e., 8 h of exposure followed by a 16 h period of no exposure).

### *Inhibition of 'B'-esterases by foliar residues of parathion*

According to the parathion transfer PBPK/PD model approximately 1.3% of the parathion residues transferred to skin (11.42 mg) produced 7.8% red blood cell AChE inhibition. Parathion in fat was capable of being further metabolized in the liver to produce additional AChE inhibition (7.8%) raising the % inhibition to 15. Additional daily exposures could conceivably result in red cell AChE inhibitions of more than 30%. Under field conditions residue levels of 0.1 to 0.09 Fg/cm$^2$ produced little or no red cell AChE inhibition over the course of several weeks or months of exposure. Results of a similar nature were obtained using the model and an 8 h exposure period.

### *Isofenphos, material balance*

The isofenphos foliar transport model utilized the 10,000 $k_d$ factor (two-sided residue) proposed by Nigg et al. (2) and supported by Harris and Solomon (11) for the transport of isofenphos residues on turf to bare feet, ankles, legs, arms and hands. The material balance data generated by the model is given at the bottom of Table 6 for a series of foliar residues (0.09, 0.1, 1.0, 5.0, and 10.0 Fg/cm$^2$) with 0.7 Fg/cm$^2$ (two-sided residue) found on isofenphos treated turf after application (11). According to the model, foliar residues of 10 Fg/cm$^2$ resulted in the transfer of 11.42 mg of isofenphos to exposed skin over the course of an 8 h day. Material balance data indicated that ~95% of the transported residue remained on the surface of the skin, ~2.5% was lost to air, ~0.56% was eliminated in urine and feces, and ~2% of the dose was retained in tissues. The dose retained in tissues was largely isofenphos present in body fat (~1%).

### *Inhibition of 'B'-esterases by turf residues of isofenphos*

The transfer of isofenphos foliar residues to skin during the work day resulted in the absorption of ~3% of the transferred dose. Approximately 43% of the absorbed dose was found in body fat as isofenphos with most of the absorbed dose (57%) being metabolized to alkyl phosphates, various carboxylic acids and 2-OH hippuric acid. The small amounts of des N-isopropyl isofenphos oxon produced during metabolism resulted in ~2% inhibition of red cell AChE. This percentage will almost double when the isofenphos residing in body fat is metabolized (total inhibition ~4%). Less than 1% red blood cell AChE inhibition was obtained when foliar residues were at or below 1.0 Fg/cm$^2$.

**Table 5.**

Percentage of enzymes inhibited by transfer of Parathion leaf residues to skin of workers

| Enz/Source | Parathion Leaf Residues, R in μg/cm$^2$ R = 10 | R = 5 | R = 1.0 | R = 0.1 | R = 0.09 |
|---|---|---|---|---|---|
| **Blood Enzymes** | | | | | |
| AChE | 7.83 | 3.94 | 0.794 | 0.0795 | 0.0716 |
| BChE | 10.42 | 5.25 | 1.056 | 0.1058 | 0.0952 |
| Dose (pmoles) | 2.74 x 10$^9$ pmoles | 1.3733 x 10$^9$ pmoles | 2.746 x 10$^8$ pmoles | 2.746 x 10$^7$ pmoles | 2.472 x 10$^7$ pmoles |
| Dose (mg/worker) | 800 mg | 400 mg | 80 mg | 8.0 mg | 7.2 mg |

**Material Balance:** lost to air, 2.12%, retained on skin, 95.2%, urine and feces, 0.415%, body tissues, 2.3%
**Metabolites:** Parathion in fat, 1.297%, p-nitrophenol, 0.211%, p-nitrophenyl sulfate, 0.136%, p-nitrophenyl glucuronide, 0.068%
BW = 70 kg, Area = 1000 cm$^2$, 8 h period of exposure

**Table 6.**

Percentage of enzymes inhibited by transfer of Isofenphos turf residues to skin.

| Enz/Source | Isofenphos Leaf Residues, R in μg/cm$^2$ R = 10 | R = 5 | R = 1.0 | R = 0.1 | R = 0.09 |
|---|---|---|---|---|---|
| **Blood Enzymes** | | | | | |
| AChE | 1.79 | 0.89 | 0.18 | 0.018 | 0.016 |
| BChE | 2.39 | 1.20 | 0.24 | 0.024 | 0.020 |
| Dose (pmoles) | 2.316 x 10$^9$ pmoles | 1.158 x 10$^9$ pmoles | 2.316 x 10$^8$ pmoles | 2.316 x 10$^7$ pmoles | 2.0845 x 10$^7$ pmoles |
| Dose (mg/worker) | 800 mg | 400 mg | 80 mg | 8.0 mg | 7.2 mg |

**Material Balance:** lost to air, 2.58%, retained on skin, 94.7%, urine and feces, 0.56%, body tissues, 2.16%
**Metabolism:** Isofenphos in fat, 1.17%, alkyl phosphates, 0.071%, carboxylic acids, 0.504%, 2-OH hippuric acid, 0.071%
BW = 70 kg, Area = 1000 cm$^2$, 8 h period of exposure

## Discussion & Conclusions

- The addition of foliar transfer coefficients to PBPK/PD models for parathion and isofenphos made it possible to reexamine the relationship between OP pesticide residues on leaf surfaces, percutaneous absorption and 'B'-esterase inhibition.
- Evaporative losses from skin were modeled according to rat and human studies.
- Equations for reactivation of inhibited enzymes were included in the model, but were not used (i.e., rates set to zero) in order to obtain maximum inhibition.
- The bimolecular inhibition rate constant for paraoxon was used for des N-isopropyl isofenphos oxon (DNIO) because a constant was not available for DNIO.
- The human foliar residue transfer- PBPK/PD parathion model (Table 5) supports the previously established reentry level of 0.09 Fg/cm$^2$ on citrus (reentry interval of 21-60 days depending upon application).
- Although a reentry interval has never been established for isofenphos residues on turf, the PBPK/PD isofenphos model (Table 6) supports the suggested reentry level of 0.6 Fg/cm$^2$.
- On the basis of ChE NOELs of 0.05 mg/kg/day for parathion and isofenphos in chronic studies, margin of exposures (MOEs) of 16 and 10, respectively, were calculated for 8 h exposures to parathion leaf residues and 2 h exposures to isofenphos turf residues.

## References


1. W.J. Popendorf and J.T. Leffingwell, Regulating OP pesticide residues for farmworker protection. *Residue Rev.*, 82, 125-201 (1982).
2. H.N. Nigg, J.H. Stamper, and R.M. Queen. The development and use of a universal model to predict tree crop harvester pesticide exposure. *Am. Ind. Hyg. Assoc. J.*, 45, 182-186 (1984).
3. J.B. Knaak M.A. Al-Bayati O.G. Raabe, and J.N. Blancato. Use of a multiple pathway and multiroute physiologically based pharmacokinetic model for predicting organophosphorus pesticide toxicity, Chapter 16, In Blancato JN, Brown RN, Dary CC and Saleh MA (Eds.) *Biomarkers for Agrochemicals and Toxic Substances*, ACS Symp. Ser., 643, Washington, D.C. (1996).
4. J.M. Gearhart, G.W. Jepson, H.J. Clewell, M.E. Andersen, and R.B. Conolly. Physiologically based pharmacokinetic model for the inhibition of acetylcholinesterase by organophosphate esters. *Environ. Health. Perspect.*, 102, 51-60 (1994).
5. K.B. Wallace and J.E. Dargan, Intrinsic metabolic clearance of parathion and paraoxon by livers from fish and rodents. *Toxicol. Appl. Pharmacol.*, 90, 235-242 (1987).
6. G.W. Jepson, D.K. Hoover, R.K Black, J.D. McCafferty, D.A. Mahle, and J.M. Gearhart, A partition coefficient determination method for nonvolatile chemicals in biological tissues. *Fundam. Appl. Toxicol.*, 22, 519-524 (1994).
7. J.B. Knaak, K. Yee, C.R. Ackerman, G. Zweig, D.M. Fry, and B.W. Wilson, Percutaneous absorption and dermal dose-cholinesterase response studies with parathion and carbaryl in the rat. *Toxicol. Appl. Pharmacol.*, 76, 252-263 (1984).
8. J.B. Knaak, M.A. Al-Bayati, O.G. Raabe, and J.N. Blancato, Development of **in vitro** $V_{max}$ and $K_m$ values for the metabolism of isofenphos by P-450 enzymes in animals and humans. *Toxicol. Appl. Pharmacol.*, 120, 106-113 (1993).
9. International Life Sciences Institute-Risk Science Institute (ILSI-RSI). Physiological parameter values for PBPK models. Report prepared under a cooperative agreement with OHEA, EPA, Washington, D.C. (1994).
10. R.T. Segawa and S.J. Powell, Monitoring the pesticide treatments of the Japanese beetle project, Sacramento County, California, 1983-1986. Volume II: Isofenphos. California Department of Food and Agriculture, Sacramento, CA (1989).
11. S.A. Harris and K.R. Solomon, Human exposure to 2,4-D following controlled activities on recently sprayed turf. *J. Environ. Sci. Health*, Part B, *Pesticides* 27, 9-22 (1992).